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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	26

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/621,593	Applicant(s) DE GROOT ET AL.	
	Examin r Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 26-37 are pending.

Applicants' traversal, the amendment to the abstract, the amendment to claims 26, 27, 28, 29, 30, 31, 32, 35, and 36, the addition of claim 37 in paper no. 25 filed on 4/30/03 is acknowledged and considered.

Claim Objections

Applicant's arguments, see paper no. 25, filed on 4/30/03, with respect to objection have been fully considered and are persuasive. The objection of claims 1 and 29 has been withdrawn because of the cancellation of claim 1 and the amendment to claim 29.

Claim 26 is objected to because of the following informalities: the phrase "animal having a genome, the genome comprising" on line 1 is redundant. Suggest replacing the phrase with -- animal whose genome comprises --.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic non-human mammalian farm animal, whose genome

comprises a stably integrated recombinant nucleic acid encoding a polymeric immunoglobulin receptor (pIgR) protein operatively linked to a mammary specific promoter, wherein said transgenic non-human mammalian farm animal over-expresses said pIgR protein in its mammary gland compared to the expression of the pIgR protein in a mammary gland of a wild-type non-human mammalian farm animal, and wherein said protein is capable of transporting a polymeric immunoglobulin protein across the basolateral side of a mammary epithelial cell to the epithelial cell's apical side in comparison to another immunoglobulin protein located on the epithelial cell's basolateral side, does not reasonably provide enablement for a transgenic mammalian farm animal whose genome comprises a recombinant nucleic acid encoding a pIgR, wherein said protein is capable of transporting a polymeric immunoglobulin protein across the basolateral side of an epithelial cell's apical side. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is directed to the making and using a transgenic mammalian farm animal whose genome comprises a stably integrated recombinant nucleic acid encoding a polymeric immunoglobulin receptor (pIgR) protein, wherein said animal over-expresses said pIgR protein compared to the expression of the pIgR protein in a wild-type animal. The invention lies in the field of producing transgenic non-human animals.

The art of record teaches how to make and use transgenic mammals whose genome expresses a heterologous gene product (US Patent No. 5,895,833).

The specification displays transgenic mice whose genome comprises a recombinant nucleic acid encoding a murine pIgR capable of transporting an immunoglobulin from a mammary epithelial cell's basolateral side to the cell's apical side (pages 2 and 3). The specification further provides teachings that pIgR is capable of transporting dimeric IgA across the epithelial cells of mucosal surfaces into the external secretions and raising the concentration of IgA relative to IgG in external secretion (pages 6 and 7).

The specification provides sufficient guidance and/or factual evidence for one skilled in the art to make and use a transgenic non-human mammalian farm animal whose genome comprises a recombinant nucleic acid encoding a polymeric immunoglobulin receptor (pIgR) protein operatively linked to a promoter, wherein said protein is over-expressed in the mammary gland of said farm animal. However, claims 26-29 embrace raising the concentration of a polymeric immunoglobulin relative compared to an immunoglobulin in an epithelial cell's basolateral side of a transgenic mammalian farm animal. The specification contemplates transporting an immunoglobulin from an epithelial layer of mucosal or glandular surfaces (GI tract, respiratory tract, genital tract and mammary gland) into the external secretions. The specification teaches over-expression of pIgR in epithelial cells in a mammary gland of a transgenic mouse. The working examples in the specification display that pIgR is exclusively found in a mammary gland when using a casein promoter. The as-filed specification lacks sufficient guidance for over-expressing pIgR in an epithelial cell (*e.g.* liver, skin, etc.) other than an epithelial cell from a mammary gland in a transgenic mammalian farm animal. The specification does not provide methods and/or materials required for one skilled in the art to reasonably extrapolate from over-expression of pIgR in epithelial cells of a mammary gland of a

transgenic mammalian farm animal to over-expressing pIgR in epithelial cells of any other organ in a transgenic mammalian farm animal. The art of record teaches that predicting transgene expression with a promoter is not predictable. See Wall (Theriogenology, 1996) who states, "Our lack of understanding of essential genetic control elements makes it difficult to design transgene with predictable behavior (page 61, last paragraph)." Also, See Houdebine discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (Journal of Biotechnology, page 275, column 1, 1994); e.g. specific promoters, presence or absence of introns, etc. In addition, the art of record teaches that hepatocytes do not express pIgR (Lamm, Am. J. Physiol, Vol. 37, G614-G617, 1998). In view of the lack of guidance provided by the specification for what type of promoter (lung-specific, liver-specific, viral promoter, etc.) could be used for over-expressing pIgR and the unpredictability of transgene expression using a promoter displayed by the art of record, it would require an undue amount of experimentation for one skilled in the art to practice the full scope of the claimed invention.

In addition, claims 26-29 recite using a nucleic acid encoding a pIgR not operatively linked to a promoter to make a transgenic mammalian farm animal. The specification provides sufficient guidance for one skilled in the art to make and/or use a recombinant nucleic acid, which comprises a promoter operatively linked to a nucleic acid encoding a pIgR protein. However, the specification fails to provide sufficient guidance and/or factual evidence for one skilled in the art to make and/or use a recombinant nucleic acid that is not operatively linked to a promoter. The teachings in the specification are directed to using a casein promoter to over-express pIgR in epithelial cells of a mammary gland in a transgenic mouse. The as-filed

specification provides guidance and/or evidence for how to make and use a recombinant nucleic acid comprising a promoter operatively linked to a nucleic acid encoding a pIgR protein to direct pIgR expression, however the claims do not recite such a structural limitation. Thus, to the extent the claims fail to recite distinguishing features to commensurate with the level of guidance presented, the claims are not considered enabled.

In addition, with respect to claims 30 and 31, directed to making a transgenic mammalian farm animal of claim 26 using a DNA construct comprising a nucleic acid encoding a pIgR protein operatively linked to a promoter capable of driving expression of said pIgR protein in a mammary gland epithelial cell, the claims are not considered enabled. The claims are not considered enabled because the transgenic mammalian farm animal in claim 26 is capable of transporting a polymeric immunoglobulin across the basolateral side of an epithelial cell's apical side, however, the transgenic mammalian farm animal produced in claims 30 and 31 can only transport pIgR protein across the mammary gland epithelial cells. The DNA construct used in the method of making in claims 30 and 31 comprises a mammary specific promoter (e.g., casein promoter). The working examples in the specification display that pIgR is exclusively found in a mammary gland when using a mammary specific promoter. The art of record does not teach using a mammary specific promoter to over-express pIgR protein in any organ other than the mammary gland. Thus, to the extent the claims fail to recite distinguishing features to commensurate with the level of guidance presented, the claims are not considered enabled.

Furthermore, with respect to claim 35, which is directed to administering a protein to enhance the expression of pIgR in a transgenic farm mammal, the specification cites that *in vitro* pIgR expression is enhanced when a protein selected from the group consisting of interferon-γ,

interleukin-1, interleukin-4, and tumor necrosis factor-α. The specification does not define what type of promoter was used for enhanced *in vitro* expression of pIgR. One skilled in the art, without evidence to the contrary, would conclude that the endogenous promoter for pIgR was used in the *in vitro* assay. The claim reads on using an antigen or interferon-γ, Il-1, Il-4, TNF-χ with any promoter (endogenous or exogenous) operatively linked to the nucleic acid encoding pIgR protein to enhance expression of pIgR in a transgenic mammalian farm animal. However, the specification fails to provide sufficient guidance for one skilled in the art to use a promoter (e.g. casein promoter, LTR promoter, etc.) to enhance pIgR expression other than the endogenous promoter for pIgR. The specification does not teach what nucleotides sequences of the endogenous promoter are considered essential for enhancing the over-expression of pIgR in the presence of the claimed proteins. In addition, the specification does not teach what promoters are able to enhance pIgR expression in the presence of the claimed proteins. The art of record does not teach what types of promoters can enhance the expression of pIgR in the presence of the claimed proteins. Thus, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from enhancing the expression of pIgR by using pIgR's endogenous promoter in the presence of the claimed proteins. Thus, in view of the lack of guidance provided by the specification the claim is not enabled.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only enable one skilled in the art to make and use a transgenic non-human mammalian farm animal, whose genome comprises a stably integrated recombinant nucleic acid encoding a polymeric immunoglobulin receptor (pIgR) protein operatively linked to a mammary specific promoter, wherein said farm animal over-expresses said pIgR protein in its

mammary gland compared to the expression of the pIgR protein in a mammary gland of a wild-type non-human mammalian farm animal, and wherein said protein is capable of transporting a polymeric immunoglobulin protein across the basolateral side of a mammary epithelial cell to the epithelial cell's apical side in comparison to another immunoglobulin protein located on the epithelial cell's basolateral side. Given the lack of sufficient guidance or direction provided the specification for the providing a mammary gland of a farm transgenic animal other then the transgenic mammalian farm animal over-expressing a pIgR in its mammary gland compared to expression of pIgR in a mammary gland of a wild-type farm mammal, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicants' disclosure.

Applicant's arguments filed 4/30/03 have been fully considered but they are not persuasive. The amendment to the claims does not overcome the rejection of claims 26-29 for making a transgenic mammalian farm animal whose genome comprises a recombinant nucleic acid encoding a pIgR not operatively linked to a promoter for the reasons set forth above under 112 first paragraph rejection. The amendment to the claims does not overcome the rejection of claims 26-29 of over-expressing pIgR protein in any epithelial cell for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 36 remains and claims 26-35 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 26-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the term "transgenic mammalian farm animal" because the claims do not define what the term embraces. The specification defines the term: Preferably, the farm-animal is an animal that can be milked. Preferably, the farm-animal is cow, a goat, a sheep, a camel, a lama and/or rabbit. With a farm animal is meant any non-human animal that is in any way commercially exploited or exploitable by man (see page 9, lines 5-11). The claim does not recite a non-human animal. It is not proper to read limitations appearing in the specification into the claim when these limitations are not recited in the claim. See MPEP 2111. It is unclear whether the term "farm" in any way limits the claim to a subgroup of mammalian animals. Any animal or mammal could be commercially exploitable by man, e.g., exotic pet industry. A human can by commercially exploited or exploitable by man, e.g., farmer, a human at a clinic for people trying to lose weight.

Applicant's arguments are moot in view of the new ground(s) of rejection.

Claims 26-29 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: active steps required for a protein **capable** of transporting a polymeric immunoglobulin across the basolateral side of an epithelial cell's apical side. The

claim does not define the active steps if the protein is not capable of transporting a polymeric immunoglobulin across the basolateral side.

Suggest amending line 3 of claim 26 to read as follows: -- protein transports a polymeric immunoglobulin protein across the basolateral side of an --.

Applicant's arguments are moot in view of the new ground(s) of rejection.

Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: active steps required for a promoter **capable** of driving expression of said pIgR protein in a mammary gland epithelial cell. The claim does not define the active steps if the promoter is not capable of driving expression of said pIgR protein in a mammary gland epithelial cell.

Suggest amending the claim 30 to read as follows: -- mammary specific promoter --.

Applicant's arguments are moot in view of the new ground(s) of rejection.

Claims 35 and 36 recite the limitation "administering an antigen to said farm animal prior to collecting the milk from the mammary gland". There is insufficient antecedent basis for this limitation in the claim. Claim 35 and 36 depend on claim 31 and claim 31 does not recite collecting milk from the mammary gland.

Applicant's arguments filed 4/30/03 have been fully considered but they are not persuasive because applicants did not address the rejection set forth above.

Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: steps required for raising the concentration of a first class immunoglobulin relative to at least a second class of immunoglobulin in a mammary gland of non-human mammalian farm animal. The step in the body of the claim is directed to producing a transgenic mammalian farm animal. This step does not complete the pre-amble of the claim.

Applicant's arguments are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 26-37 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 26-37 encompasses any transgenic farm animal, the scope of which encompasses a human being, which is non-statutory subject matter. As such, the recitation of the limitation "non-human" would be remedial. See 1077 O.G. 24, April 21, 1987.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER